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(54) Title: QUINOLINE-2-CARBOXYLIC ACID DERIVATIVE AND ITS USE AS EXCITATORY AMINO ACIDS ANTAGONIST

(57) Abstract

The (+) enantiomer of E 4-(4-Acetylaminophenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydro quinoline 2-carboxylic acid and salt thereof which are antagonist of excitatory amino acids, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

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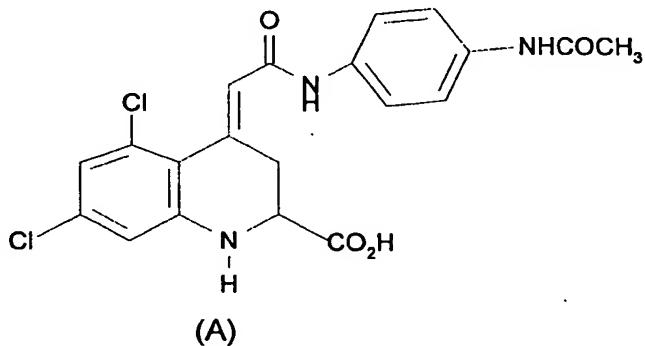
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## QUINOLINE-2-CARBOXYLIC ACID DERIVATIVE AND ITS USE AS EXCITATORY AMINO ACIDS ANTAGONIST

This invention relates to an enantiomer of ( $\pm$ ) E 4-(4-Acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydro quinoline 2-carboxylic acid a potent and specific antagonist of excitatory amino acids, to processes for preparing the same, to pharmaceutical compositions containing it, to its use in medicine.

WO 97/12870 describes inter alia ( $\pm$ ) E 4-(4-Acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydro quinoline - 2-carboxylic acid (A)



and salts thereof, which have an antagonist action at the strychnine insensitive glycine binding site located on the N-methyl-D- aspartate (NMDA) receptor complex.

We have now found that an enantiomer of compound (A) herein after referred to as the (+) enantiomer exhibits a particular useful profile of activity as a selective antagonist for the strychnine insensitive glycine binding site on the NMDA receptor complex.

The present invention thus provides the (+) enantiomer of (E) 4-(4-acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydro quinoline 2-carboxylic acid (hereinafter compound (I)) and salts thereof, substantially free of the corresponding (-) enantiomer.

The term substantially free as used herein means that compound (I) contains less than 10% of the (-) enantiomer and preferably less than 5%.

5 The term (+) enantiomer as used herein refers to the specific enantiomer which is the product of examples 2, 4 and 5.

For use in medicine the salts of compound (I) will be physiologically acceptable thereof. Other salts however may be useful in the preparation of compound I or physiologically acceptable salts thereof. Therefore, unless otherwise stated, references to salts include both physiologically acceptable salts and non-physiologically acceptable salts of compound (I).

10 Suitable physiologically acceptable salts of compounds of the invention include base addition salts.

15 Suitable physiologically acceptable base addition salts of compound (I) include alkali metal or alkaline earth metal salts such as sodium, potassium, calcium, and magnesium, and ammonium salts, formed with amino acids (e.g. lysine and arginine) and organic bases (e.g. procaine, 20 phenylbenzylamine, ethanolamine diethanolamine and N-methyl glucosamine).

A preferred salt of compound (I) is the sodium salt.

25 The compound of the invention and/or physiologically acceptable salts thereof are excitatory amino acid antagonists. More particularly they are potent antagonists at the strychnine insensitive glycine binding site associated with the NMDA receptor complex. As such it is a potent antagonist of the NMDA receptor complex. Compound (I) is therefore 30 useful in the treatment or prevention of neurotoxic damage or neurodegenerative diseases. Thus compound (I) is also useful for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, haemorrhagic stroke, cerebral ischemia, cerebral vasospasm, hypoglycemia, amnesia, hypoxia, anoxia, perinatal 35 asphyxia cardiac arrest. Compound I is also useful in the treatment of

chronic neurodegenerative diseases such as Huntingdon's disease, Alzheimer's senile dementia, amyotrophic lateral sclerosis, Glutaric Aciduria type, multi-infarct dementia, status epilepticus, contusive injuries (e.g. spinal cord injury and head injury), viral infection induced 5 neurodegeneration (e.g. AIDS, encephalopathies), Down syndrome, epilepsy, schizophrenia, depression, anxiety, pain, neurogenic bladder, irritative bladder disturbances, migraine, headaches, including cluster headaches, tension headache, drug dependency, including withdrawal symptoms from alcohol, cocaine, opiates, nicotine, benzodiazepine and 10 emesis.

The potent and selective action of the compound of the invention at the strychnine- insensitive glycine binding site present on the NMDA receptor complex may be readily determined using conventional test 15 procedures. Thus the ability to bind at the strychnine insensitive glycine binding site was determined using the procedure of Kishimoto H et al. J Neurochem 1981, 37 1015-1024. The selectivity of the action of compound (I) for the strychnine insensitive glycine site was confirmed in studies at other ionotropic known excitatory amino acid receptors. Thus 20 compound (I) was found to show little or no affinity for the kainic acid (kainate) receptor,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor or at the NMDA binding site.

The compound of the invention has also been found to inhibit NMDA 25 induced convulsions in mice using the procedure Chiamulera C. et al. Psychopharmacology (1990) 102, 551-552.

The neuroprotective activity of the compound of the invention was demonstrated in the middle cerebral artery occlusion preparation in 30 mice, using the procedure described by Chiamulera C. et al., European Journal of Pharmacology, 216 (1992) pp. 335-336.

The invention therefore provides for the use of compound (I) and/or physiologically acceptable salt thereof for use in therapy and in

particular use as medicine for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

5 The invention also provides for the use of compound (I) and/or a physiologically acceptable salt thereof for the manufacture of a medicament for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

10 According to a further aspect, the invention also provides for a method for antagonising the effects of excitatory amino acids upon the NMDA receptor complex, comprising administering to a patient in need thereof an antagonistic amount of compound (I) and/or a physiologically acceptable salt.

15 It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

20 It will further be appreciated that the amount of the compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800mg per day, 25 dependent upon the route of administration.

Thus for parenteral administration a daily dose will typically be in the range 20-800mg, preferably 60-800mg per day. For oral administration a daily dose will typically be within the range 200-800mg, e.g. 400-600mg per day.

30 The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, compound (I) may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

5 The invention thus further provides a pharmaceutical formulation comprising compound (I) or a physiologically acceptable salt thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

10 15 The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant, or rectal administration. Parenteral administration is preferred.

20 Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatine, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants

for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p- hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as 5 cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

- 10 The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution 15 with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.
- 20 For administration by inhalation compound (I) according to the invention is conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide or other suitable propellants, such as 25 dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide or other suitable gases, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.
- 30 Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable carrier such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges

of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

5 The composition according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion 10 exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

15 The compositions according to the invention may contain between 0.1 - 99% of the active ingredient, conveniently from 30- 95% for tablets and capsules and 3-50% for liquid preparations.

In a further aspect the invention provides processes for the preparation of compound 1.

20 Thus in a first process (hereinafter Process A) compound (I) ((+)-E-4-(4-Acetylamino-phenylcarbamoylmethylene)-5,7- dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid) may be prepared by esterification of compound A with a suitable chiral alcohol, separating the resultant diastereomeric esters by conventional means e.g. chromatography or 25 crystallisation followed by hydrolysis of the required single diastereomeric ester.

30 Suitable chiral alcohols for use in the process A include (+)S-indanol, (+)S-methyl mandelate, chiral (C1-4)alkyl lactate: i.e., (+)R or (-)S methyl lactate, (+)R t-butyl lactate, (+)R or (-)S ethyl lactate, (-)S isopropyl lactate, (-)S butyl lactate, (+)R isobutyl lactate or chiral aralkyl lactate (i.e. benzyl lactate), (-)S perillyl alcohol, (-)methyl(R)-3-hydroxy-2-methylpropionate, (-)(R)-2-butanol, (-)(S)-2-methyl-1-butanol.

The diastereomeric esters of compound A including the single diastereomeric ester substantially free of the other diastereomeric are novel compounds and represent a further aspect of the invention

5 The diastereomeric esters of compound A may be prepared by conventional means such as reaction of the chiral alcohol with an activated derivative of the compound A in an aprotic solvent such as ether e.g. tetrahydrofuran. The activated derivative of Compound A may be prepared from compound A using conventional means for 10 preparing activated derivatives of a carboxylic acid groups such as those conveniently used in peptide synthesis.

15 A particularly convenient method of preparing the diastereomeric esters of compound A is to prepare the activated derivative of compound A in the presence of the chiral alcohol.

20 Thus for example compound A may be treated with the Mitsunobu combination of reagents, i.e. a dialkyl azo-dicarboxylate such as diethylazodicarboxylate and a triarylphosphine e.g. triphenylphosphine or trialkylphosphine (i.e. tributylphosphine) in the presence of the chiral alcohol.

25 The reaction conveniently takes place in the presence of a suitable solvent such as an ether (e.g. diethylether or tetrahydrofuran), a halohydrocarbon (e.g. dichloromethane) or a nitrile (e.g. acetonitrile) or a mixture thereof at a temperature ranging from 0-30°.

30 The required single diastereomeric ester of compound A substantially free of the other diastereomers may be obtained from the mixture thereof by conventional means, for example by the use of conventional chromatographic procedures such as preparative HPLC or by fractional crystallization.

35 Compound (I) may be prepared from the corresponding single diastereomeric ester of compound A by hydrolysis e.g. alkaline

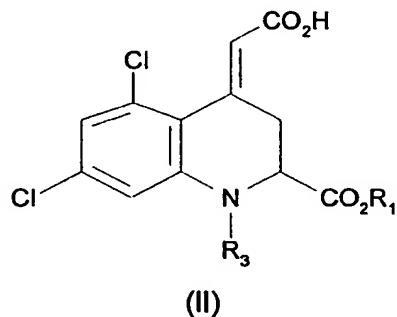
hydrolysis. Thus for example the hydrolysis may be carried using an alkali metal hydroxide e.g. sodium hydroxide or lithium hydroxide in a solvent such as an ether e.g. tetrahydrofuran and water.

Compound (I) may be isolated as the free acid or as a salt thereof.

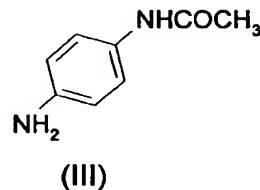
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Compound I may also be obtained from racemic compound A by use of chiral HPLC procedures.

Compound (A) may be prepared by reaction of an activated derivative of the carboxylic acid (II) in which  $R_1$  is a carboxylic acid protecting group and  $R_3$  is hydrogen or a nitrogen protecting group

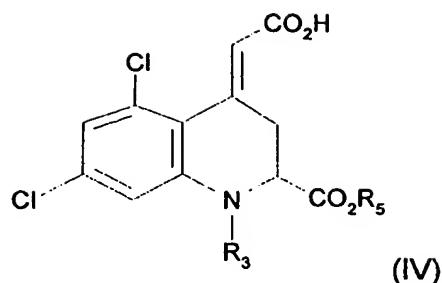


15 with the amine(III)

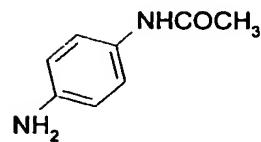


followed where necessary by subsequent removal of the carboxylic acid 20 protecting group  $R_1$  and any nitrogen protecting group  $R_3$  using the methods and examples described in WO97/12870.

The invention also provides a further process for the preparation of the compound (I) (hereinafter process B) which comprises reacting an activated derivative of the carboxylic acid (IV) in which  $R_3$  is hydrogen 25 or a nitrogen protecting group and  $R_5$  is a suitable chiral group with the amine (III).



5



(III)

10 and subjecting the resulting compound to the following reactions:

- where necessary removal of nitrogen protecting group  $R_3$
- separation of the resultant diastereomeric esters
- hydrolysis of the required single diastereomeric ester and isolation of the (+) enantiomer as a free acid or a salt thereof, and if desired the subsequent conversion of the free acid of the (+) enantiomer into a salt thereof.

15

Suitable chiral groups ( $R_5$ ) for use in the process B are those derived from chiral alcohols such as (+)S-indanol, (+)S-methyl mandelate, chiral  
 20 (C1-4)alkyl lactate: i.e., (+)R or (-)S methyl lactate, (+)R t-butyl lactate, (+)R or (-)S ethyl lactate, (-)S isopropyl lactate, (-)S butyl lactate, (+)R isobutyl lactate or chiral aralkyl lactate (i.e. benzyl lactate), (-)S perillyl alcohol, (-)methyl(R)-3-hydroxy-2-methylpropionate, (-)(R)-2-butanol, (-) (S)-2-methyl-1-butanol.

25

$R_5$  is preferably a group derived from a chiral (C1-4)alkyl lactate alcohol.

More preferably  $R_5$  is derived from  $(+)(R)$  t-butyl lactate alcohol.

Suitable activated derivatives of the carboxylic acid group include the corresponding acyl halide, mixed anhydride, activated ester such as a thioester or the derivative formed between the carboxylic acid group and a coupling agent, such as that used in peptide chemistry, for example carbonyl diimidazole or a diimide, such as dicyclohexylcarbodiimide.

The reaction is preferably carried out in an aprotic solvent, such as a hydrocarbon, a halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran.

When  $R_3$  is a nitrogen protecting group, examples of suitable groups include alkoxy carbonyl, e.g. t-butoxycarbonyl, arylsulphonyl e.g. phenylsulphonyl or 2-trimethylsilylethoxymethyl.

Alkyl when used as substituent or a part of a substituent group means that the group may be straight or branched. Thus C1-4 alkyl includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or ter-butyl.

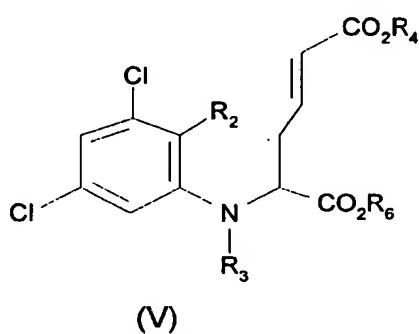
The activated derivatives of the carboxylic acid (IV) may be prepared by conventional means. A particularly suitable activated derivative for use in this reaction is thioester such as that derived from pyridine-2-thiol. These esters may conveniently be prepared by treating the carboxylic acid (II) with 2,2'-dithiopyridine and triphenylphosphine in a suitable aprotic solvent such as an ether e.g. tetrahydrofuran, a halohydrocarbon e.g. dichloromethane, an amide e.g. N,N-dimethylformamide or acetonitrile.

The appropriate diastereomeric derivative can be isolated by conventional means e.g. chromatography or by crystallisation.

The hydrolysis step conveniently takes place using an alkali metal hydroxide e.g. sodium hydroxide or lithium hydroxide in a suitable solvent such as an ether i.e. tetrahydrofuran, water and a mixture

thereof or alkali trialkylmethylsilanolate (e.g. trimethylsilanolate) followed, where desired or necessary, by the addition of a suitable acid e.g. hydrochloric acid to give the corresponding free carboxylic acid.

5 Compounds of formula (IV) or (II) may be prepared by the cyclisation of a compound of formula (V)



10 in which  $R_2$  represents a bromine or iodine atom,  $R_3$  represents hydrogen or a nitrogen protecting group,  $R_4$  represents a hydrogen atom or a suitable carboxylic acid protecting group such as t-butyl group and  $R_6$  represents  $R_1$  or  $R_5$  as defined in formula (II) or formula (IV) respectively, followed by removal of the of carboxylic protecting group  
 15  $R_4$  using conventional methods.

In one embodiment of this process the reaction may be carried out using a catalytic amount of a Palladium (O) complex such as tetrakis(triphenylphosphine)palladium and a suitable organic base such  
 20 as trialkylamine e.g. triethylamine or inorganic base, e.g. potassium carbonate.

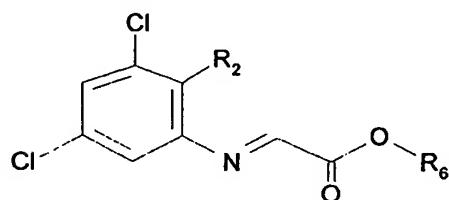
The reaction is conveniently carried out in an aprotic solvent such as acetonitrile or dimethylformamide at a temperature with the range of 20°C to 150°C followed, where necessary or desired, by subsequent  
 25 removal of the carboxylic acid protecting group  $R_4$  and any protecting group  $R_3$ .

In a further embodiment of the process the reaction is carried out using a catalytic amount of a Pd(II) salt such as palladium acetate, in the presence of a suitable organic base such as trialkyl amine e.g.  
 30 triethylamine and of a triarylphosphine such as triphenylphosphine.

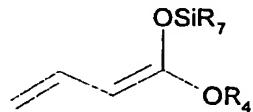
5 The reaction is carried out in an aprotic solvent such as acetonitrile or dimethylformamide and preferably with heating, followed, where necessary or desired, by subsequent removal of the carboxylic acid protecting group  $R_4$  and any nitrogen protecting group  $R_3$ .

10 Compounds of formula (V) may be prepared by reacting a imino ester of formula(VI), wherein  $R_2$  and  $R_6$  have the meanings defined above, with a compound of formula (VII) in which  $R_7$  represents a C1-4 alkyl group and  $R_4$  is a hydrocarbysilyl group such as trialkylsilyl, e.g. trimethylsilyl or terbutyldimethylsilyl or a suitable carboxylic acid protecting group such as tert-butyl group, followed, if desired, by the conversion of the group NH into a nitrogen protecting group  $NR_3$ .

15



(VI)



(VII)

20

The reaction is carried out in an aprotic solvent such as halohydrocarbon e.g. dichloromethane, chlorobenzene or acetonitrile at low temperature e.g. -78°C in the presence of a Lewis acid such as zinc bromide and zinc chloride.

25

The conversion of the group NH into the nitrogen protected group  $NR_3$  may be obtained using conventional means for introducing such nitrogen protecting groups, e.g. reaction with the group  $R_3X$  wherein X is a leaving group e.g. halogen or methanesulphonate.

30

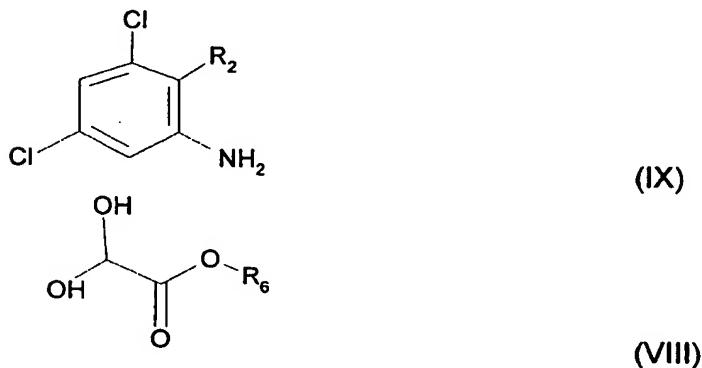
The process for preparing compounds of formulae (II) or (IV), using the intermediate (V) when prepared from intermediates (VI) and (VII), is novel and forms a further feature of the invention.

A particularly preferred embodiment of this novel process for preparing compounds of formula (V) is to use an intermediate ester (VI), wherein R<sub>6</sub> group is derived from (+)R t-butyl lactate alcohol. This yields a mixture of diastereomeric esters in which the required diastereomeric ester is obtained in diastereomeric excess.

Further, the cyclisation of the compound (V) so obtained using the process conditions described above affords the required compound (IV) as a mixture of diastereomeric esters in which the required diastereomeric ester is also obtained in diastereomeric excess.

Compounds of formula (VI) may be prepared by reaction of amine (IX) with a compound of formula (VIII) wherein R<sub>2</sub>, R<sub>6</sub> have the meanings defined for compounds of formula (V).

15



The reaction is preferably carried out in a solvent such as an aromatic hydrocarbon (e.g. benzene toluene or xylene) at a temperature ranging from ambient to the reflux temperature of the reaction mixture.

Compounds of formula (III), (VII), (VIII), and (IX) are either known compounds or may be prepared by analogous methods to those used for known compounds.

Thus compounds of formula (VII) may be prepared according to procedures described in *Tetrahedron Letters*, Vol. 22, No. 29, pp. 2833 -

2836, 1981. Compounds of formula (VIII) may be prepared according to procedures described in Helvetica Chimica Acta, 1981 Vol. 64, p. 2808.

5      In any of the above reactions the carboxylic acids protecting group may be removed by conventional procedures known for removing such groups. Thus compounds where  $R_1$  is a benzyl group, this may be removed by hydrolysis using an alkali metal hydroxide e.g. lithium hydroxide or sodium hydroxide in a suitable solvent such as ethanol or isopropanol, water or mixtures thereof, followed, where desired or necessary, by that addition of a suitable acid e.g. hydrochloric acid to give the corresponding free carboxylic acid.

10     When  $R_4$  is a t butyl group this may be removed by hydrolysis using organic acids e.g. formic acid.

15     In any of the above reactions the nitrogen protecting group may be removed by conventional procedures known for removing such groups, for example by acid or base hydrolysis. Thus when  $R_3$  is alkoxy carbonyl e.g. t-butoxycarbonyl or phenylsulphonyl it may be removed by alkaline hydrolysis using for example lithium hydroxide in a suitable solvent such as tetrahydrofuran or an alkanol e.g. isopropanol. Alternatively the alkoxy carbonyl group may be removed by acid hydrolysis.

20     Physiologically acceptable salts of compound I may be prepared by treating the corresponding acid with an appropriate base in a suitable solvent. For example alkali and alkaline metal salts may be prepared from an alkali or alkaline metal hydroxide, or the corresponding carbonate, bicarbonate or trialkylsilanolate e.g. trimethylsilanolate thereof.

25     Alternatively alkali or alkaline earth salts may be prepared by direct hydrolysis of carboxylic acid protected derivatives of compound I with the appropriate alkali or alkaline metal hydroxide.

30     In order that the invention may be more fully understood the following examples are given by way of illustration only.

35

**In the Intermediates and Examples unless otherwise stated:**

5 Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refers to 0°C. Infrared spectra were measured on a FT-IR instrument. Proton Magnetic Resonance (<sup>1</sup>H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me<sub>4</sub>Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd),  
10 triplets (t), quartets (q) or multiplets (m). Column chromatography was carried out over silica gel (Merck AG Darmstaadt, Germany). The following abbreviations are used in text: EA = ethyl acetate, CH = cyclohexane, DCM = dichloromethane; THF = tetrahydrofuran, TFA = trifluoroacetic acid, TEA = triethylamine, DMSO = dimethylsulphoxide,  
15 TLC refers to thin layer chromatography on silica plates. Solutions were dried over anhydrous sodium sulphate; r.t. (RT) refers to room temperature.

**Intermediate 1****-tert-butyl-(R)-acryloyloxy-2-methylacetate**

20 To a solution of (R)-*tert*-butyl lactate alcohol (4.5 g), triethylamine (9.5 ml) and dimethylaminopyridine (0.73 g) in dry dichloromethane (200 ml) was added, at 0°C, a solution of acryloyl chloride (5.5 ml) in dichloromethane (100 ml), and the resulting mixture was stirred for 1 hr  
25 at 0°C and for an additional hour at room temperature. Then a 1M solution of HCl was added followed by ethyl acetate (600 ml). The organic phase was washed with water and brine. Final purification by column chromatography (cyclohexane/ethyl acetate 85/15) afforded the title compound (4.6 g) as a colourless oil.

30 <sup>1</sup>H NMR (DMSO) (ppm) 6.36 (dd, 1H), 6.22 (dd, 1H), 5.99 (dd, 1H), 4.89 (q, 1H), 1.40 (d, 3H), 1.39 (s, 9H)  
IR (CDCl<sub>3</sub>) (cm<sup>-1</sup>) 1727

**Intermediate 2**

**1-tert-butyl-(R)-2(ox acetoxy)-2-methyl ac tate**

5 A solution of intermediate 1 (4.6 g) in THF/H<sub>2</sub>O (3/1) (28 ml) was reacted overnight at room temperature with osmium tetroxide (4% wt in water, 5 ml) and sodium periodate (12.3 g). The mixture was taken up with ether (500 ml), the water phase was separated, and the organic phase was dried and concentrated. Final purification by column chromatography (cyclohexane/ethyl acetate 60/40) afforded the title compound (4.1g) as a colourless oil.

10 <sup>1</sup> H NMR (DMSO): 6.75 (d, 1H); 6.70 (d, 1H); 5.05 (t, 1H); NMR - 4.85m (1H); 1.40m(12H).

**Intermediate 3****(3,5-dichloro-iodophenylimino)acetic acid, 1-(R)-(1-tert-butoxycarbonyl)ethyl ester**

15 A solution of intermediate 2 (0.784 g) in toluene (20 ml) was refluxed in Dean-Stark apparatus for 1hr. Then, 3,5-chloro-2-iodoaniline (0.75 g) and MgSO<sub>4</sub> (5 g) was added, and the mixture refluxed for 1hr. Then mixture was cooled, filtered through celite to eliminate the MgSO<sub>4</sub>, concentrated to give the title compound (1.2 g) as a pale yellow oil.

20 <sup>1</sup> H NMR (DMSO) (ppm) 7.95 (s, 1H); 7.67 (d, 1H); 7.30 (d, 1H); 5.09 (q, 1H); 1.49 (d, 3H); 1.43 (s, 9H)  
IR (Film) (cm<sup>-1</sup>) 1743

**Intermediate 4****(E)-5-(3,5-dichloro-iodophenylimino)hex-2-enedioic acid, 6-[1-(R)-(1-tert-butoxycarbonyl)]-ethyl ester**

25 To a suspension of ZnCl<sub>2</sub> (0.36g) in dry dichloromethane (10ml) cooled to -78°C, a solution of intermediate 3 (1.2g) in dry dichloromethane (20ml) was added. Then 1,1 trimethylsilyloxy 1,3 butadiene (1.14g) was added and the resulting mixture was stirred for 2hrs at -30°C. Then a saturated solution of NH<sub>4</sub>Cl (20ml) was added followed by ethyl acetate (30ml). The organic phase was washed with brine (20ml) and dried. Purification by column chromatography (cyclohexane/ethyl acetate 50/50) afforded the title compound (1.13g) as a colourless oil (diastereomeric excess 50%).

<sup>1</sup> H NMR (DMSO) d (ppm) 12.3 (bs, 1H) 7.01 (d, 1H); 6.79 (m, 1H); 6.66 (d, 1H); 5.90 (d, 1H); 5.29 (d, 1H); 4.97 (q, 1H); 4.72 (m, 1H); 2.83 (m, 2H); 1.39 (m, 12H).

5      **Intermediate 5**

**(E)-4-carboxymethylene-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, [1-(R)-(1-tert-butoxycarbonyl)]ethyl ester**

To a solution of intermediate 4 (1.2g) in dry DMF (10ml) was added TEA (0.7ml) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.248g). The reaction mixture was heated to 100°C for 1 hour, then ethyl acetate (20ml) was added followed by a 1M solution of HCl (10ml). The organic phase was washed with brine (20ml), dried and concentrated. Final purification by column chromatography (cyclohexane/ethyl acetate 40/60) afforded the title compound (0.5g) as a colourless oil (diastereomeric excess 50%).

15

<sup>1</sup> H NMR (DMSO) 12.3 (s, 1H); 7.27 (bs, 1H); 6.73 (d, 1H); 6.45 (d, 1H); 6.40 (s, 1H); 4.79 (q, 1H); 4.29 (m, 1H); 3.61 (m, 1H); 3.13 (m, 1H); 1.35 (m, 10H).

20

**Intermediate 6**

**(E)-4-[(2-pyridyl)thiocarbonylmethylene]-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, [1-(R)-(1-tert-butoxycarbonyl)]ethyl ester**

To a solution of intermediate 5 (0.5g) in dry THF (30ml) was added PySSPy (0.66g) and PPh<sub>3</sub> (0.81g). The reaction mixture was stirred for 1h at room temperature, then the solvent was evaporated and the crude purified by column chromatography (cyclohexane/ethyl acetate 80/20) to give the title product (0.170g) as a yellow foam (diastereomeric excess 60%).

30

<sup>1</sup> H NMR (DMSO) p.p.m 8.61 (m, 1H); 7.91 (m, 1H); 7.71 (m, 1H); 7.46 (bs, 1H); 7.45 (m, 1H); 6.88 (s, 1H); 6.78 (d, 1H); 6.76 (d, 1H); 4.81 (q, 1H); 4.36 (m, 1H); 3.73 (dd, 1H); 3.05 (m, 1H); 1.4 (m, 3H); 1.34 (s, 9H).

35

**Example 1**

**(+/-)(E)-4-acetylamino-phenylcarbamoylmethylen )-5,7-dichloro-1,2,3,4-tetrahydro quinoline-2-carboxylic acid**  
**(diastereomers 1a and 1b)**

5 A solution of diethylazodicarboxylate (0.136ml;) in dry tetrahydrofuran (10ml) was added, dropwise over 5 minutes, to a suspension of  $(\pm)(E)$ -4-(4-acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (270mg), triphenylphosphine (228mg) and tert-butyl (R)-(+)-lactate (127mg) in dry tetrahydrofuran (20ml) under a nitrogen atmosphere.

10 The yellow solution was stirred at 23°C for 30 minutes, then concentrated *in vacuo* and purified by flash chromatography eluting with cyclohexane/ethyl acetate 4:6 to give 240mg of the title compound (a mixture of the two diastereoisomers 1a and 1b). The diastereomers were separated by preparative HPLC (column:Supelcosil LC-CN; phase

15 hexane-tetrahydrofuran 65:35 and after 14 minutes 60:40; flux 10ml/min;  $\lambda=260\text{nm}$ ) and then further purified on silica, eluting with cyclohexane/ethyl acetate, first 8:2 then 1:1, to give diastereoisomer 1a :91mg as whitish solid, and diastereoisomer 1b 76mg as yellow solid

Example 1: m.p.175-177°C. IR (nujol): 3200 (NH), 1738 (C=O)  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (DMSO): 10.09-10.05 (2s, 1H); 9.86-9.84 (2s, 1H); 7.64-7.44 (m, 4H); 7.34-7.19 (2d, 1H); 6.73-6.66 (d, 2H); 6.71-6.64 (2s, 1H); 4.76-4.56 (2q, 1H); 4.39-4.26 and 3.73 (m and dd, respectively, 2H); 3.30-2.68 (dd, 1H); 2.00 (s, 3H); 1.34-1.31 (2s, 9H); 1.29-1.15 (2d, 3H). MS:  $m/z=562 [\text{M}+\text{H}]^+$

20 Diastereomer 1a m.p. 206-8°C. T.l.c.ethyl acetate-cyclohexane 7:3, Rf= 047. IR (nujol): 3314 (NH), 1730, 1666, 1656 (C=O)  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (DMSO): 10.09 (s, 1H); 9.86 (s, 1H); 7.57 (d, 2H); 7.49 (d, 2H); 7.33 (d, 1H); 6.71 (d, 2H); 6.67 (d, 1H); 6.65 (m, 1H); 4.57 (q, 1H); 4.37 (m, 1H); 4.29 (m, 1H); 2.69 (m, 1H); 2.00 (s, 3H); 1.35 (s, 9H); 1.16 (d, 3H). MS:  $m/z=561 [\text{M}]^+$ , 562  $[\text{M}+\text{H}]^+$ . HPLC: retention time 12.56min (column:Supelcosil LC-CN; phase hexane-tetrahydrofuran 70:30; flux 0.8ml/min;  $\lambda=260\text{nm}$ )

25 Diastereomer 1b: m.p. 105-7°C. T.l.c.ethyl acetate-cyclohexane 7:3, Rf= 040. IR (nujol): 3310 (NH), 1738 and 1659 (C=O)  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (DMSO): 10.05 (s, 1H); 9.85 (s, 1H); 7.55 (d, 2H); 7.47 (d, 2H); 7.19 (d,

30

35

1H); 6.74 (d, 1H); 6.73 (d, 1H); 6.72 (s, 1H); 4.77 (q, 1H); 4.29 (m, 1H);  
3.74 (dd, 1H); 3.29 (m, 1H); 2.00 (s, 3H); 1.32 (s, 9H); 1.29 (d, 3H). MS:  
5  $m/z=561[M]^+$ , 562 [M+H] $^+$ . HPLC: retention time 15.60min  
(column:Supelcosil LC-CN; phase hexane-tetrahydrofuran 70:30; flux  
0.8ml/min;  $\lambda=260\text{nm}$ )

### Example 2

**(+)-E-4-(4-Acetylamino-phenylcarbamoylmethylene)-5,7- dichloro-  
1,2,3,4-tetrahydroquinoline-2-carboxylic acid**

10 Lithium hydroxide monohydrate (12.84mg) was added to a solution of  
diastereoisomer 1a (from Example 1 86mg) in tetrahydrofuran (5ml) and  
water (2.5ml). The solution was stirred at 23°C for 30 minutes, then  
concentrated *in vacuo*. The residue was diluted with further water (10ml)  
15 and extracted with ethyl acetate (2X15ml). The aqueous layer was  
acidified with 5% hydrochloric acid until pH=1 and extracted with ethyl  
acetate (3X15ml). The combined organic extracts were dried and  
concentrated *in vacuo* to give the title compound as a whitish solid  
(56mg). m.p. 224-6°. IR (nujol): 3356-3302 (NH), 3350-2600 (OH); 1724  
and 1663-1650 (C=O)  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (DMSO): 12.71 (s, 1H); 10.10 (s,  
20 1H); 9.87 (s, 1H); 7.56 (d, 2H); 7.50 (d, 2H); 7.10 (d, 1H); 6.70 (d, 2H);  
6.68 (m, 1H); 4.11 (m, 1H); 3.87 (m, 1H); 3.08 (dd, 1H); 2.01 (s, 3H).  
MS:  $m/z=434$  [M+H] $^+$ .  
HPLC: retention time 15.2 min (column:cyclbond I 2000 SN ; phase  $\beta$ -  
cyclodextrin S Naphthyl ethyl carbamate, phase mobile: methanol buffer  
25 ammonium acetate (pH=3); flux 1ml/min. ;  $\lambda=260$  nm)  
[ $\alpha$ ]<sub>D</sub>=[+16]<sub>20</sub>  $\lambda= 598\text{nm}$ , solvent :dimethyl sulphoxide.  
Conc=0.26% w/v

### Example 3

**(E)-4-(4-acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-  
1,2,3,4-tetrahydroquinoline-2-carboxylic acid,[1-(R)-(1-tert-  
butoxycarbonyl)]ethyl ester**

30 To a solution of intermediate 6 (0.155g) in dry toluene (20ml) 4-  
aminoacetanalide (0.05g) was added. The resulting mixture was heated  
35 at 100°C for 3hrs, then the solvent was evaporated and the crude

purified by column chromatography (cyclohexane/ethyl acetate 50/50) to give the title compound (0.05 g) as a yellow solid.

5       $^1\text{H-NMR}$  (DMSO) d 10.05 (bs, 1H); 9.85 (bs, 1H); 7.55 (d, 2H); 7.47 (d, 2H); 7.19 (dd, 1H); 6.74 (d, 1H); 6.73 (d, 1H); 6.72 (s, 1H); 4.77 (q, 1H); 4.29 (m, 1H); 3.74 (dd, 1H); 3.29 (m, 1H); 2.00 (s, 3H); 1.32 (s, 9H); 1.29 (d, 3H).  
IR (nujol) ( $\text{cm}^{-1}$ ) 3310, 1738, 1659.

#### Example 4

10     (+)(E)-4-(4-acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid.

To a solution of example 3 (0.021g) in THF/ $\text{H}_2\text{O}$  (3/1) LiOH (0.005g) was added. After 15mins. the THF was evaporated and water (2ml) was added. The solution was washed with ethylacetate (2x5ml), then a 1M solution of HCl was added and the resulting solution was extracted with ethyl acetate (2x5ml) and evaporated to give the title compound as a pale yellow solid (0.01g).

15      $^1\text{H-NMR}$  (DMSO) d 12.71 (s, 1H); 10.10 (s, 1H); 9.87 (s, 1H); 7.56 (d, 2H); 7.50 (d, 2H); 7.10 (d, 1H); 6.70 (d, 2H); 6.68 (m, 1H); 4.11 (m, 1H); 3.87 (m, 1H); 3.08 (dd, 1H); 2.01 (s, 3H).

20     IR (nujol) ( $\text{cm}^{-1}$ ) 3356-3302, 1724, 1663-1650.

HPLC: retention time 9.7 min (column: cyclobond SN; phase  $\beta$ -cyclodextrin S Naphthyl carbamate, phase mobile: methanol buffer ammonium acetate (pH=5); flux 1ml/min. ;  $\lambda=260$  nm)

25

#### Example 5

(+)-4-(4-Acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, sodium salt

Sodium trimethylsilanolate (7.74 mg) was added to a suspension of (+) 30 4-(4-acetylamino-phenylcarbamoylmethylene)-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (30 mg) in dry tetrahydrofuran (3 ml) under a nitrogen atmosphere. The yellow suspension was stirred at 23°C for 1 hr, then it was concentrated *in vacuo* and the residue was triturated with diethyl ether (5 ml). After filtration the title compound was 35 obtained (27 mg) as a yellow solid.

M.p. 202-5 °C (dec).

IR (nujol): 3400-3000 (NH), 1650 (C=O)  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (DMSO): 11.71 (bs, 1H); 9.26 (bs, 1H); 7.65 (d, 2H); 7.49 (d, 2H); 6.74 (d, 1H); 6.71 (bs, 1H); 6.52 (s, 1H); 6.50 (d, 1H); 3.51 (m, 1H); 3.29 (m, 1H); 2.64 (m, 1H); 5 2.01 (s, 3H). MS:  $m/z$ =456 [M+H] $^+$ , 478 [M+H] $^+$ . HPLC: retention time 14.28 min.(column: cyclobond I 2000SN; phase b-cyclodextrin S Naphtyl ethyl carbamate, phase mobile: methanol-buffer ammonium acetate, flux 1ml/min;  $\lambda$ =260nm).

10 **Pharmacy Example**

	<b>Intravenous Infusion</b>	<b>% w/v</b>
	Compound (I)	0.3 - 0.5
15	Polysorbate 80	1
	tris(hydroxymethyl)aminomethane	0.54
	Dextrose solution 5% w/v	qs to volume

20 Compound (I) and Polysorbate were added to a solution of tris(hydroxymethyl)aminomethane in a 5% aqueous dextrose solution suitable for injection. The solution was filtered through a sterile 0.2 micron sterilising filter and filled in containers before being sterilised by autoclaving.

25 The affinity of the compound of the invention for strychnine insensitive glycine binding site located on the NMDA receptor complex was determined using the procedure of Kishimoto H. et al J. Neurochem 1981, 37, 1015-1024. The pKi value obtained is 8.8.

## Claims

1. (+) (E)4-(4-Acetylamino-phenylcarbomoylmethylene) -5,7-dichloro-1,2,3,4-tetrahydro quinoline 2-carboxylic acid, substantially free of the (-) enantiomer, and salts thereof.

5

2. (+) (E)4-(4-Acetylamino-phenylcarbomoylmethylene) -5,7-dichloro-1,2,3,4-tetrahydro quinoline 2-carboxylic acid, substantially free of the (-) enantiomer, and physiologically acceptable salts thereof.

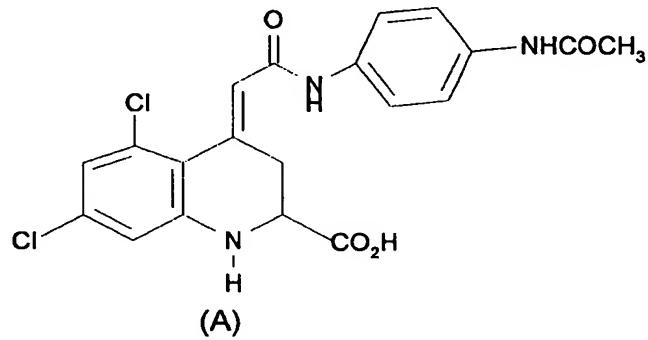
10

3. The sodium salt of (+) (E)4-(4-Acetylamino-phenylcarbomoylmethylene) -5,7-dichloro-1,2,3,4-tetrahydro quinoline 2-carboxylic acid, substantially free of the (-) enantiomer.

15

4. A process for preparation of a compound as claimed in any of claims 1 to 3 which comprises:

a) esterification of compound A with a suitable chiral alchool,



20 followed by

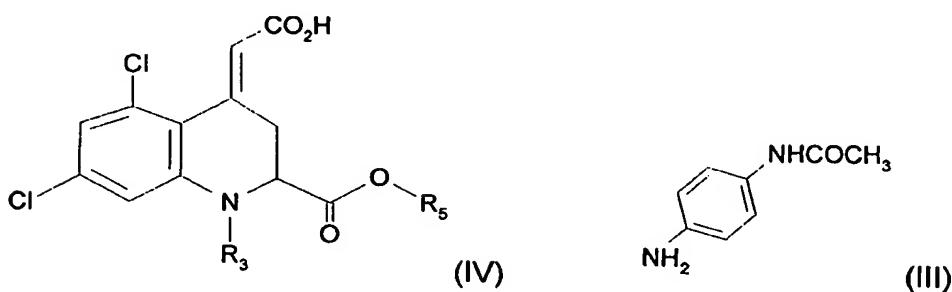
i) separation of the resultant diastereomeric esters,

ii) hydrolysis of the required single diastereomeric ester, and isolation of the (+) enantiomer as the free acid or a salt thereof; and if desired the subsequent conversion of the free acid of the (+) enantiomer into a salt thereof;

25

b) reacting a compound of formula(IV), wherein  $R_3$  is hydrogen or a nitrogen protecting group and  $R_5$  is a suitable chiral group, with the amine(III),

5

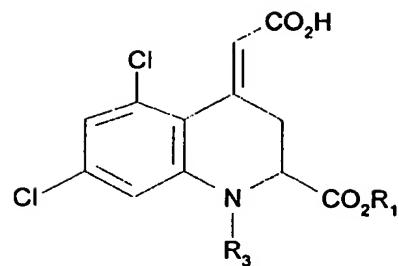


in the presence of a Lewis acid and subjecting the resulting compounds  
10 to the following reactions:

i) where necessary removal of nitrogen protecting group  $R_3$ ,  
ii) separation of the resultant diastereomeric esters,  
iii) hydrolysis of the required single diastereomeric ester and isolation of  
15 the (+) enantiomer as the free acid or a salt thereof; and if desired the  
subsequent conversion of the free acid into a salt thereof.

5. A process as claimed in claim 4 wherein the chiral alcohol is (+)R t-butyl lactate alcohol, or  $R_5$  is a group derived from (+)R t-butyl lactate alcohol.

20 6. A process for the preparation of intermediates of formula (IV), as defined in claim 4 or 5, or intermediates of formula (II)



(II)

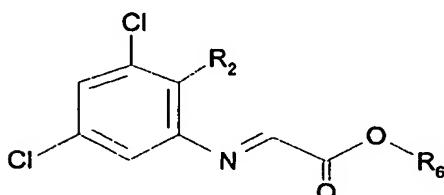
5 which comprises the following steps:

i) reacting an imino ester of formula (VI), wherein  $R_2$  represents a bromine or iodine atom and  $R_6$  is a suitable chiral group  $R_5$  as defined above or a carboxylic acid protecting group  $R_1$  as described in formula (II), with a compound of formula (VII) in which  $R_7$  represents a  $C_{1-4}$  alkyl group and  $R_4$  is a hydrocarbysilyl group or a suitable carboxylic acid protecting group, followed, if desired, by the conversion of the resultant compound of formula (V) wherein  $R_3$  is hydrogen into a compound of formula (V) wherein  $R_3$  is a nitrogen protecting group and

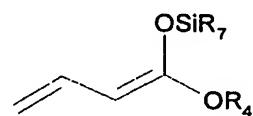
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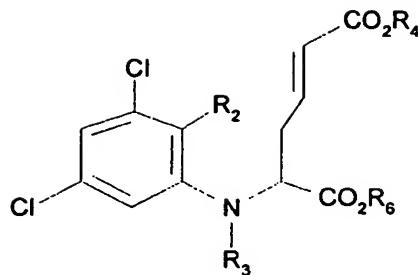


(VI)



(VII)

ii) cyclisation of the resulting compound (V)



(V)

5 in which R<sub>2</sub> is a bromine or iodine atom, R<sub>3</sub> represents hydrogen or a  
nitrogen protecting group R<sub>4</sub> is a hydrogen atom or a suitable carboxylic  
acid protecting group and R<sub>6</sub> represents a suitable chiral group R<sub>5</sub> or a  
carboxylic acid protecting group R<sub>1</sub> and thereafter, if necessary,  
removing the carboxylic protecting group R<sub>4</sub> and any nitrogen  
10 protecting group R<sub>3</sub>.

7. A process as claimed in claims 4 or 5 wherein the intermediate (IV) is prepared according to the process of claim 6.

15 8. A pharmaceutical composition comprising a compound as claimed in claim 2 or claim 3 in admixture with one or more physiologically acceptable carriers or excipients.

20 9. The use of a compound as claimed in claim 2 or claim 3 in the manufacture of a medicament for antagonising the effect of excitatory amino acids upon the NMDA receptor complex.

10. A compound as claimed in claim 2 or claim 3 for use in therapy.

25 11. A method of treatment of a mammal including man for conditions where antagonising the effects of excitatory amino acids on the NMDA receptor complex is of therapeutic benefit comprising administration of an effective amount of a compound as claimed in claim 2 or claim 3 .

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/01700

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C07D215/48 A61K31/47 C07B57/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C07D A61K C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 386 839 A (MERCK SHARP & DOHME LTD.) 12 September 1990 see the whole document, particularly examples 156-158 ---	1-11
A	BRANDSTADTER S M ET AL.: "Reactions of ketene silyl acetals with imine-complexes of titanium tetrachloride. New and convenient route to 5,6-dihydro-2-pyridones and 5-amino-2-alkenoates" TETRAHEDRON LETTERS, vol. 28, no. 6, 1987, pages 613-6, XP002074162 Oxford, GB see the whole document ---	6 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

11 August 1998

Date of mailing of the international search report

21/08/1998

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**INTERNATIONAL SEARCH REPORT**

International Application No	
PCT/EP 98/01700	

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 97 12870 A (GLAXO WELLCOME S.P.A.) 10 April 1997 cited in the application see the whole document, particularly page 4, lines 14-19, and example 5 -----	1-11
P, X	WO 98 07704 A (GLAXO WELLCOME S.P.A.) 26 February 1998 see the whole document, particularly page 18, lines 10-22 -----	6

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 98/01700

### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 11 because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark:** Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/01700

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